Remarks

Claims 19-24, 27-46, and 49-64 are pending in the application. Claims 23, 31-44, 46 and 57-64 are currently amended. Claims 23, 31-44 and 46 have been amended to correct typographical errors and to include a definition of variable *m* used in the groups -$(CH_2)_mC(O)NR^2R^2$ and -$(CH_2)_mC(=W)$-$NH(CH_2)_p$-(amino acid) for substituent R^3. Support for this amendment is found on page 25, line 25 of the specification. Claims 57-64 have been amended to present the claims in independent form. New claim 65, which depends from any one of claims 57-64, has been added. Support for claim 65 is found in the specification on page 13, lines 14-16 and on page 14, lines 3-4. No new subject matter has been added to the claims. Applicants reserve the right to present any canceled subject matter in one or more continuation or divisional applications.

Claim Objections

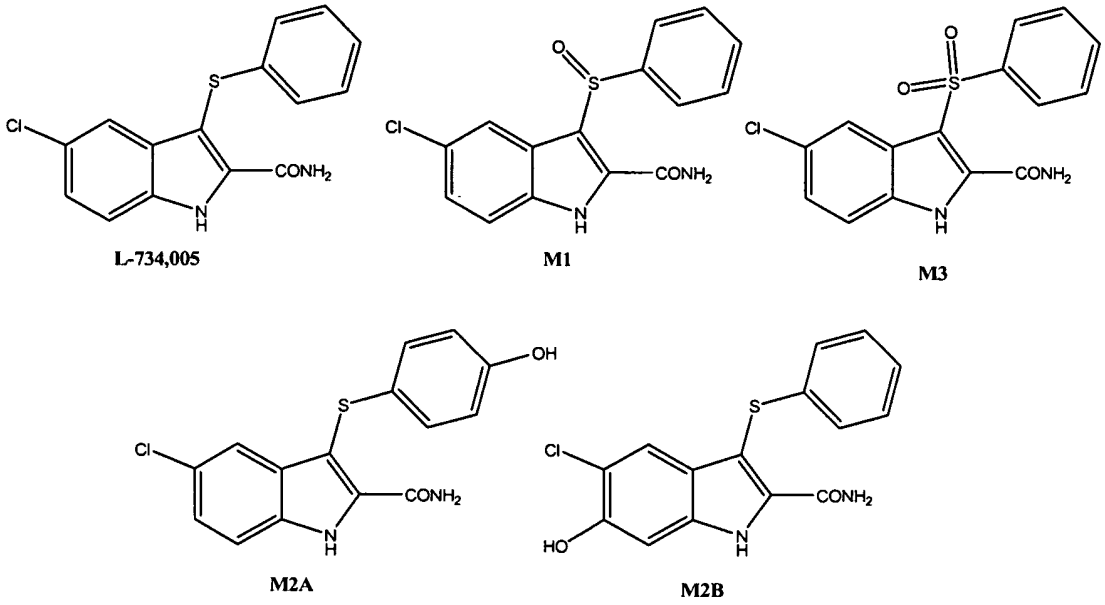
The Examiner has objected to claims 57-64 because they depend from rejected claims 19 and 24. Claims 57-64 have been amended to present the claims in independent form, as suggested by the Examiner. Claims 57-64 are therefore in condition for allowance.

Claim Rejections under 35 U.S.C. § 103

The Examiner has maintained the rejection of claims 19-24, 27-32, 45, 47-51 and 53-56 under 35 U.S.C. §103(a) as unpatentable over U.S. Patent No. 5,527,819 to Williams et al. (Williams). The Examiner asserts that the compounds recited in the claims are obvious homologs of the compounds disclosed by Williams. Applicants respectfully disagree. As discussed in the response to the Office Action mailed November 3, 2005, Williams teaches inhibition of HIV reverse transcriptase using substituted indole compounds that are either unsubstituted or mono-substituted on the phenyl ring of the indole. All of the compounds disclosed by Williams contain a single substituent at the 5-position of the indole ring. The compounds recited in the claims of the present application are limited to compounds that have at least two substituents on the phenyl ring of the indole. Applicants submit that the art of phenylindole inhibitors of HIV-1 reverse transcriptase is highly unpredictable, and that it would not be obvious to one skilled in the art that phenylindole compounds with at least two non-

hydrogen substituents on the phenyl ring of the indole would be significantly active against HIV. This can be seen from the data presented in Table 3 on page 89 of the specification, which shows the influence of modifying the substituents on the phenyl ring of the indole. As Table 3 shows, varying the position of the substituents on the ring can significantly influence the activity of the compounds. For example, a change in the substitution pattern in the indole by only one carbon, from 5,6-dichloro (compound 9) to 5,7-dichloro (compound 10), increases the EC_{50} by a factor of 53 from 0.03 μM to 1.6 μM. This substantial change in biological activity is solely due to the position of the second chloride on the ring, since the other substituents on the indole are equivalent. Table 3 also highlights that the type of substituents on the phenyl ring have a considerable impact on the activity of the compounds. Changing the substitution on the phenyl ring of the indole from 5,7-difluoro (compound 13) to a 5,7-dichloro (compound 10) changes the EC_{50} by a factor of 160, from EC_{50} 0.01 μM to EC_{50} 1.6. Changing a 5,6-difluoro substituted indole (compound 12) to a 5,6-dichloro substituted indole (compound 9) results in a change of EC_{50} by a factor of at least 10. The results presented in Table 3 show that the activity of the compounds that are di-substituted on the phenyl ring of the indole are highly unpredictable.

As the Examiner notes, the article "Biotransformation of 5-Chloro-3-phenylthioindole-2-carboxamide (L-734,005) in Rhesus Monkeys and Rat Liver Microsomes to a Potent HIV-1 Reverse Transcriptase Inhibitor" *Drug Metab. Disp.*, 21(4), 598-604, Jul.-Aug. 1993 by Balani *et al.* discloses metabolites M1, M2A, M2B and M3 of 2-carboxamido-3-phenylthio-5-chloroindole, compound L-734005, that are isolated form monkey plasma and rat liver microsomal incubates. The structures of these compounds are shown below.



Balani discloses that the sulfoxide metabolite M1 is approximately one-half as active as the parent sulfide L-734,005. In contrast, further oxidation of the sulfur to the sulfone metabolite M3 increases the activity to approximately 7 times more active than the parent compound. One would not predict that the compound M3 at the sulfone oxidation level would be more active based on the initial decrease in activity when the sulfur is oxidized to the sulfoxide M1. This disclosure further underlines the unpredictable nature of the biological activity of substituted phenyl indoles.

Balani further discloses that metabolite isolate M2, which includes compounds M2A and M2B, was found to be "relative inactive" (page 600, column 1). The only difference between compound M2B and the parent compound L-734,005, is that M2B is substituted at the 6-position of the indole with a hydroxyl group in addition to the 5-chloro substituent of the parent compound. Therefore, Balani teaches that relative to the parent compound, di-substitution of the phenyl of the indole ring results in diminished activity. The Examiner points out that compounds M2B and L-734,005 are not equivalent to the compounds claimed in the present application or to those disclosed by Williams. However, this difference would not cause a person skilled in the art to ignore the treaching of Balani, as the Office Action suggests. The disclosure of Balani teaches that within structurally similar compounds, i.e. 3-thiophenyl substituted indoles with all other structural components remaining the same, additional substitution at the phenyl ring of the indole results in a drop of activity. Based on the teaching of Balani, a person of ordinary skill in the art

the art would be directed away from modifying related sulfoxide or sulfone compounds with di-substitution on the phenyl ring of the indole, as recited in the present claims.

The disclosure of Balani as well as the data presented in Table 3 of the specification show that the art of substituted indole anti-HIV compounds is highly unpredictable.

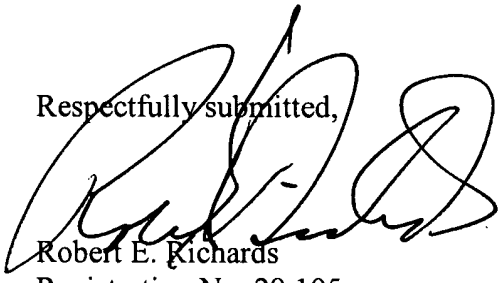
It is noted that "[w]here structural similarity of the claimed compound to the prior art compound is not evidenced by such recognized tests of presumptive equivalence as isomerism or homology and the applicant points out functional group and property differences not possessed by the prior art compounds, these facts outweigh the bare opinion of the examiner that the compounds are structurally similar and thus unpatentably obvious." *In re Grose et al.*, (CCPA 1979) 592 F.2d 1161, 201 USPQ 57; *Ex parte Knowles et al.* (POBA 1957) 122 USPQ 15.

Applicants submit that the Examiner has not considered the teaching of the art as a whole and the unpredictable nature of the claimed compounds. In the absence of hindsight, there is no suggestion or motivation to make the compounds recited in the claims. In fact, Balani teaches away from the present invention. When the teachings of the art as a whole are considered, it is submitted that Claims 19-24, 27-32, 45, 47-51 and 53-56 are patentable over Williams. Therefore, withdrawal of the rejection of the claims under 35 U.S.C. § 103 in view of Williams is respectfully requested.

Conclusion

Applicants respectfully submit that the current amendments overcome the Examiner's rejections. Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and remarks. The Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account 11-0980.

Respectfully submitted,



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